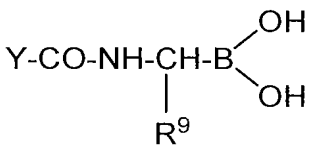
Amendments to the Claims

The listing of claims will replace all prior versions, and listings of claims in the application.

1. (Original) A pharmaceutically acceptable base addition salt of a boronic acid of formula (I):



(I)

wherein

Y comprises a hydrophobic moiety which, together with the aminoboronic acid residue -NHCH(R^9)-B($OH)_2$, has affinity for the substrate binding site of thrombin; and

R^9 is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is 3, 4, 5 or 6 or R^9 is -$(CH_2)_m$-W where m is 2, 3, 4 or 5 and W is -OH or halogen.

2. (original) The salt of claim 1 wherein R^9 is an alkoxyalkyl group.

3. (original) The salt of claim 1 wherein YCO- comprises an amino acid residue which binds to the S2 subsite of thrombin, the amino acid residue being N-terminally linked to a moiety which binds the S3 subsite of thrombin.

4. (currently amended) The salt of claim 1 wherein ~~Y~~ YCO comprises a dipeptide which binds to the S3 and S2 binding sites of thrombin.

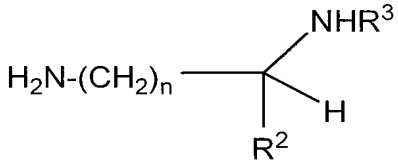
5. (currently amended) The salt of claim 4 wherein the S3-binding amino acid residue is of (R)-configuration, the S2-binding residue is of (S)-configuration, and the fragment -NHCH(R^9)-$B(OH)_2$ is of (R)-configuration.

6. (original) The salt of claim 5 wherein R^9 is an alkoxyalkyl group.

7. (original) The salt of claim 1 wherein the boronic acid has a Ki for thrombin of about 100 nM or less.

8. (original) The salt of claim 1 wherein the salt comprises a salt of the boronic acid with metal or a strongly basic organic nitrogen-containing compound.

9. (original) The salt of claim 1 wherein the salt comprises a salt of the boronic acid with an alkali metal, an aminosugar, a guanidine or an amine of formula (XI):



(XI)

where n is from 1 to 6, R^2 is H, carboxylate or derivatised carboxylate, R^3 is H, C_1-C_4 alkyl or a residue of a natural or unnatural amino acid.

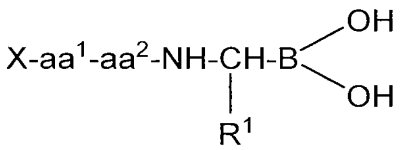
10. (original) The salt of claim 4 wherein the Y dipeptide is N-terminally protected or N-terminally unprotected, and the peptide linkages in the dipeptide are unsubstituted or independently N-substituted by a C_1-C_{13} hydrocarbyl, wherein the C_1-C_{13} hydrocarbyl contains no heteratoms or at least one in-chain or in-ring nitrogen, oxygen or sulfur atom, and the C_1-C_{13} hydrocarbyl is unsubstituted or substituted by a substituent selected from halo, hydroxy and trifluoromethyl.

11. (currently amended) The salt of claim 1 wherein the salt consists essentially of ~~an acid~~ a salt in which one B-OH group of formula (I), when trigonally represented, remains protonated.

12. (original) The salt of claim 5 which comprises boronate ions derived from the peptide boronic acid and has a stoichiometry consistent with the boronate ions carrying a single negative charge.

13. (original) The salt of claim 6 which consists essentially of a monosodium or monolithium salt of the boronic acid.

14. (original) A pharmaceutically acceptable base addition salt of a boronic acid of formula (II):



(II)

where:

X is H or an amino-protecting group;

aa^1 is an amino acid residue having a hydrocarbyl side chain containing no more than 20 carbon atoms and comprising at least one cyclic group having up to 13 carbon atoms;

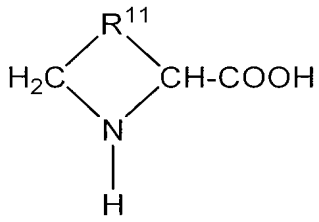
aa^2 is an imino acid residue having from 4 to 6 ring members;

R^1 is a group of the formula $-(CH_2)_s-Z$, where s is 2, 3 or 4 and Z is -OH, -OMe, -OEt or halogen.

15. (previously presented) The salt of claim 14 wherein aa^1 is selected from Phe, Dpa and wholly or partially hydrogenated analogues thereof.

16. (original) The salt of claim 15 wherein aa^1 is of R-configuration.

17. (original) The salt of claim 14 wherein aa^2 is a residue of an imino acid of formula (IV)



(IV),

where R^{11} is $-CH_2-$, $-CH_2-CH_2-$, $-S-CH_2-$, $-S-C(CH_3)_2-$ or $-CH_2-CH_2-CH_2-$, and, when the formula (IV) ring is 5- or 6-membered, the formula (IV) ring is unsubstituted or is substituted at one or more $-CH_2-$ groups by from 1 to 3 C_1-C_3 alkyl groups.

18. (original) The salt of claim 17 wherein aa^2 is of S-configuration.

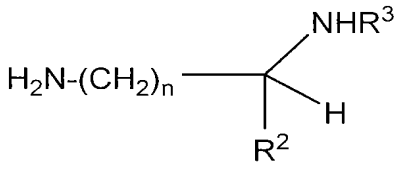
19. (original) The salt of claim 14, wherein aa^1-aa^2 is (R)-Phe-(S)-Pro and the fragment $-NH-CH(R_1)-B(OH)_2$ is of R-configuration.

20. (currently amended) The salt of claim 15 wherein the boronic acid is of formula (VIII):

X-(R)-Phe-(S)-Pro-(R)-boroMpg-OH~~Mpg-B(OH)$_2$~~ (VIII),

wherein X is R^6-$(CH_2)_p$-C(O)-, R^6-$(CH_2)_p$-$S(O)_2$-, R^6-$(CH_2)_p$-NH-C(O)- or R^6-$(CH_2)_p$-O-C(O)-, wherein p is 0, 1, 2, 3, 4, 5 or 6 and R^6 is H or a 5 to 13-membered cyclic group which is unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen; amino; nitro; hydroxy; a C_5-C_6 cyclic group; C_1-C_4 alkyl or C_1-C_4 alkyl containing, or linked to the cyclic group through, an in-chain O atom, the aforesaid alkyl groups optionally being substituted by a substituent selected from halogen, amino, nitro, hydroxy or a C_5-C_6 cyclic group; and boroMpg-OH is a residue of an aminoboronic acid of the formula H_2N-CH($(CH_2)_3$OMe)$B(OH)_2$.

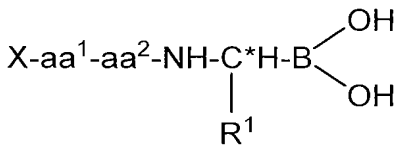
21. (original) The salt of claim 15 wherein the salt comprises a salt of the boronic acid with an alkali metal, an aminosugar or an amine of formula (XI):



(XI)

where n is from 1 to 6, R^2 is H, carboxylate or derivatised carboxylate, R^3 is H, C_1-C_4 alkyl or a residue of a natural or unnatural amino acid.

22. (original) A pharmaceutical product comprising a therapeutically effective amount of a boronate salt which consists essentially of a single base addition salt of a boronic acid formula (XX):



(XX)

where:

X is H or an amino-protecting group;

aa^1 is an amino acid residue of R-configuration having a hydrocarbyl side chain containing no more than 20 carbon atoms and comprising at least one cyclic group having up to 13 carbon atoms;

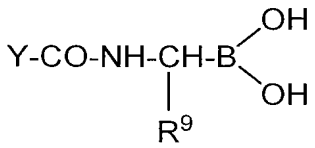
aa^2 is an imino acid residue of S-configuration having from 4 to 6 ring members;

C* is a chiral centre of R-configuration; and

R^1 is a group of the formula $-(CH_2)_s-Z$, where s is 2, 3 or 4 and Z is -OH, -OMe, -OEt or halogen.

23. (previously presented) A pharmaceutical formulation adapted for oral administration, comprising

a) a first species selected from a boronic acid of formula (I), or said boronic acid when in the form of boronate ions of said boronic acid, or equilibrium forms of said boronic acid and said boronate ions, or combinations thereof:



(I)

wherein

Y comprises a hydrophobic moiety which, together with the aminoboronic acid residue $-NHCH(R^9)-B(OH)_2$, has affinity for the substrate binding site of thrombin; and

R^9 is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is 3, 4, 5 or 6 or R^9 is $-(CH_2)_m-W$ where m is from 2, 3, 4 or 5 and W is -OH or halogen; and

(b) a second, pharmaceutically acceptable, species selected from metal ions and basic organic nitrogen containing compounds having a pKb of about 7 or more.

24. (withdrawn) A method of inhibiting thrombin in the prophylaxis or therapy of disease, comprising orally administering to a mammal suffering from, or at

risk of suffering from, thrombosis a therapeutically effective amount of the salt defined in claim 1.

25. (withdrawn) A method for preventing thrombosis in a haemodialysis circuit of a patient, for preventing a cardiovascular event in a patient with end stage renal disease, for preventing venous thromboembolic events in a patient receiving chemotherapy through an indwelling catheter, for preventing thromboembolic events in a patient undergoing a lower limb arterial reconstructive procedure, or for treating by way of therapy or prophylaxis an arterial disease selected from acute coronary syndromes, cerebrovascular thrombosis, peripheral arterial occlusion and arterial thrombosis resulting from atrial fibrillation, valvular heart disease, arterio-venous shunts, indwelling catheters or coronary stents, the method comprising orally administering to a mammal a therapeutically effective amount of the salt defined in claim 16.

26. (original) An oral pharmaceutical formulation, comprising a therapeutically effective amount of the salt of claim 1.

27. (original) A medicament adapted for oral administration and comprising a therapeutically effective amount of a pharmaceutically acceptable base addition salt of a boronic acid which is a selective thrombin inhibitor and has a neutral aminoboronic acid residue capable of binding to the thrombin S1 subsite linked through a peptide linkage to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites,

the salt comprising a cation having a valency n and having an observed stoichiometry consistent with a notional stoichiometry (boronic acid:cation) of n:1.

28. (original) The medicament of claim 27 wherein the boronic acid has a Ki for thrombin of about 100 nM or less.

29. (withdrawn) A method for making a salt of claim 1, comprising:

combining in a solvent diethanolamine and an ester of a boronic acid as defined in claim 1;

allowing or causing a precipitate to form and recovering the precipitate;

converting the precipitated material into the free organoboronic acid by contacting the precipitated material with an aqueous acid or base; and

reacting the organoboronic acid with a base of a pharmaceutically acceptable base to form ~~to~~ a salt as defined in claim 1.

30. (previously presented) The salt of claim 1, wherein the salt is a metal salt.

31. (previously presented) The salt of claim 1, wherein the salt is an alkali metal salt.

32. (previously presented) The salt of claim 31, wherein the alkali metal salt is a sodium salt.

33. (currently amended) The salt of claim 1, wherein the salt is an alkaline earth metal salt.

34. (currently amended) The salt of claim 33, wherein the alkaline earth metal salt is a calcium salt.

35. (currently amended) The salt of claim 20, wherein the salt is an alkaline earth metal salt.

36. (currently amended) The salt of claim 35, wherein the alkaline earth metal salt is a calcium salt.

37. (previously presented) The salt of claim 35, wherein the boronic acid is of the formula Cbz-(R)-Phe-(S)-Pro-(R)- Mpg-$B(OH)_2$.

38. (currently amended) The salt of claim 37 wherein the salt ~~is~~ comprises a salt of the formula ~~[~~{Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-$B(OH)(O^-)$}$]_2Ca^+$ where the symbol -B(OH)(O-) refers to the corresponding tetrahedral boronyl groups as well as the trigonal boronyl group.

39. (new) The salt of claim 4 wherein R^9 is methoxypropyl.

40. (new) The salt of claim 14 wherein aa^1 is of (R)-configuration, aa^2 is of (S)-configuration and the fragment $-NH-CH(R^1)-B(OH)_2$ is of (R)-configuration.

41. (new) The salt of claim 40 wherein R^1 is methoxypropyl.

42. (new) The salt of claim 41 which is an alkali or alkaline earth metal salt.

43. (new) The salt of claim 1 which is not an ammonium or choline salt.

44. (new) The salt of claim 1 which comprises anhydride species of the boronic acid.

45. (new) The salt of claim 1 which is an alkali metal salt of a boronic acid of the formula Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-$B(OH)_2$.

46. (new) The salt of claim 45 which comprises anhydride species of the boronic acid.

47. (new) The salt of claim 40 wherein Z is -OMe or -OEt and which is not an ammonium or choline salt and which comprises anhydride species of the boronic acid.

48. (new) The salt of claim 40 wherein aa^1 is (R)-Phe or (R)-Dpa, aa^2 is (S)-Pro or (S)-azetidine-2-carboxylic acid and R^1 is methoxypropyl.

49. (new) The salt of claim 40 wherein Z is -OMe or -OEt and which is not an ammonium or choline salt and is in a pharmaceutically acceptable aqueous solution.

50. (new) The salt of claim 49 which is a salt of an alkali metal, an alkaline earth metal or a strongly basic organic compound.

51. (new) The salt of claim 49 wherein the organic compound is an aminosugar, lysine or arginine.

52. (new) A sodium salt of a boronic acid of the formula Cbz-(R)-Phe-(S)-Pro-(R)-boroMpg-OH, wherein boroMpg is a residue of an aminoboronic acid of the formula $H_2N\text{-}CH((CH_2)_3OMe)B(OH)_2$.

53. (new) The salt of claim 52 which is in a pharmaceutically acceptable aqueous solution.

54. (new) The salt of claim 52 which comprises anhydride species of the boronic acid.

55. (new) The salt of claim 52 which is the monosodium salt.

56. (new) The salt of claim 55 which is the solid phase.

57. (new) A composition of matter which is pharmaceutically acceptable and has the characteristics of a product obtained by contacting a boronic acid of the formula Cbz-(R)-(Phe)-(S)-Pro-(R)-Mpg-$B(OH)_2$ and a pharmaceutically acceptable base selected from alkali metal bases, alkaline earth metal bases, aminosugars, lysine and arginine.

58. (new) The composition of matter of claim 57 which is in the solid phase.

59. (new) The composition of matter of claim 57 when comprised in a pharmaceutical formulation.

60. (new) The composition of matter of claim 57 wherein the base is a sodium base and wherein the composition of matter is in the solid phase.

61. (new) The composition of matter of claim 57 wherein the base is a sodium base and wherein the composition of matter is in the form of a pharmaceutically acceptable aqueous solution.

62. (new) A pharmaceutical formulation comprising in the solid phase a compound which is a source of boronate species corresponding to the acid Cbz-(R)-Phe-

(S)-Pro-(R)-Mpg-$B(OH)_2$ and a source of pharmaceutically acceptable cations other than choline and ammonium.

63. (new) The formulation of claim 62 wherein the cations are alkali metal ions.

64. (new) The formulation of claim 62 wherein the cations are sodium ions.